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# Human Gene Therapy: Application, Ethics and Regulation

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# NOTABLE STUDENT WORKS*

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## I. Introduction

On September 14, 1990, Drs. R. Michael Blaese,[1] W. French Anderson[2] and Kenneth W. Culver[3] opened the door on a new age of medical treatment when they injected a four-year-old girl who suffers from adenosine deaminase deficiency (ADA),[4] a rare genetic disorder, with blood cells containing genetic material designed to correct her genetic disease. The child is scheduled to return for monthly treatments for two years following the procedure,[5] but it is

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* These student-written articles were chosen anonymously by the Notes Editor.

1. Chief of the National Cancer Institute's Cellular Immunology Section.

2. Chief of the National Heart, Lung and Blood Institute's Laboratory of Molecular Hematology.

3. Senior Clinical Investigator at the National Cancer Institute.

4. The disease is caused by a lack of the ADA gene, which creates an enzyme that removes dangerous metabolic byproduct from the body. If the byproducts are not removed, they will break down the immune system. The disease is similar to the disease that affected a Texas boy who was confined to a plastic bubble to protect him from infection. The girl in the study has not been confined to a bubble because she was able to receive injections of a synthetic version of the enzyme. Natlie Angier, *Girl, 4, Becomes First Human to Receive Engineered Genes*, N.Y. TIMES, Sept. 15, 1990, at A1.

5. Virginia Baskerville, *Human Gene Therapy Becomes a Reality*, NIH OBSERVER, Vol. 1, No. 6, at 3 (Nov./Dec. 1990) [hereinafter *Human Gene Therapy Becomes Reality*]. The first official reports of the preliminary findings from the study were submitted to the FDA on December 13, 1990. These preliminary findings indicate that the genetic material injected into the patient is functioning as expected and that the patient's immune system may even be able to fight off a common bacteria. Natalie Angier, *Gene-Treated Girl Is Raising Hopes*, N.Y. TIMES, Dec. 14, 1990, at A24. In addition, the only side effect that the patient has experienced came after her third monthly treatment when her cheeks flushed and her temperature rose 0.5 degrees C. Virginia Baskerville, *Progress Beautiful in First Gene Trial*, NIH OBSERVER, Vol. 2, No. 1, at 1 (Jan./Feb. 1991).

the hope of the doctors that the new genetic material injected into the girl's blood will begin to produce copies of the ADA gene and, in so doing, create a functioning immune system.[6] This experiment marks the first time that doctors have attempted to combat a genetic disease in humans through the use of gene therapy.[7] As scientists learn more about the human genome[8] and the genetic basis of disease, the number of applications for this type of therapy will grow.[9] Researchers already have announced the discovery of the genetic origins of diseases such as sickle cell anemia,[10] cystic fibrosis,[11] and osteoarthritis.[12] Recent studies also indicate that diabetes,[13] Alzheimer's disease,[14] and all types of tumors[15] have a genetic basis.

In addition, on January 29, 1991, Dr. Steven A. Rosenberg[16] performed gene therapy on two patients suffering from metastatic melanoma, a lethal type of skin cancer.[17] The process used in the melanoma patients was similar to that used in the patient with ADA except that the gene injected in the cancer study is designed to produce a tumor-destroying enzyme.[18] Recently, Dr. Rosenberg began a

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6. Larry Thompson, *Human Gene Therapy Debuts at NIH*, WASH. POST, Sept. 15, 1990, at A1.

7. Angier, *supra* note 4, at A1; *see also* Thompson, *supra* note 6, at A1.

8. The genome is the term used to refer to the complete set of hereditary factors contained in the chromosomes. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (26th ed. 1981).

9. Dr. Blaese believes that human gene therapy will develop to the point at which physicians will keep genetic material in an office refrigerator, and the infusion process will be conducted in the doctor's office. Blaese admits that this is a long way off, but he is confident that his vision will become a reality in the next century. *Human Gene Therapy Becomes Reality*, *supra* note 5, at 6.

As of January 1992, not quite a year and a half since the first gene therapy trial, eleven more trials have been approved by the NIH and seven more are under consideration. Robin Herman, *Gene Therapy Is No Longer a Rarity*, WASH. POST, Jan. 21, 1992, at 7. In addition, the NIH and the FDA recently cleared the way for the first commercially run clinical trial using gene therapy. The trial will be conducted by targeted Genetics Corporation and will test the application of human gene therapy in AIDS patients. Andrew Pollack, *Gene Therapy Gets the Go-Ahead*, N.Y. TIMES, Feb. 14, 1992, at D1.

10. W. French Anderson and John C. Fletcher, *Gene Therapy In Human Beings: When Is It Ethical To Begin?*, 303 NEW ENG. J. MED. 1293 (1980).

11. Natalie Angier, *Flawed 2-in-1 Protein Causes Cystic Fibrosis*, N.Y. TIMES, Feb. 26, 1991, at C3; *see also* Jean Seligmann, *Curing Cystic Fibrosis?*, NEWSWEEK, Oct. 1, 1990, at 64.

12. Osteoarthritis is the most common form of arthritis. Elizabeth Rosenthal, *Genetic Link Suggested in One Form of Arthritis*, N.Y. TIMES, Sept. 5, 1990, at A18.

13. *Gains Cited in Genetic Research on Diabetes*, N.Y. TIMES, Feb. 15, 1991, at A17.

14. Gina Kolata, *Alzheimer's Researchers Close in on Causes*, N.Y. TIMES, Feb. 26, 1991, at C1.

15. Natalia Angier, *Gene That Checks Cell Growth May Be Key to Many Cancers*, N.Y. TIMES, April 23, 1991, at C1.

16. Chief of the National Cancer Institute's Surgery Branch.

17. Natalie Angier, *For First Time, Gene Therapy Is Tested on Cancer Patients*, N.Y. TIMES, Jan. 30, 1991, at A1. Dr. Rosenberg's study is the first use of gene therapy in patients with cancer.

18. *Id.* The cells are called tumor-infiltrating lymphocytes (TIL) and are created using

second experimental procedure to combat malignant melanoma.[19] In this new procedure, Dr. Rosenberg removes cells from the patient's tumors, adds genes from a naturally occurring anti-tumor toxin,[20] and then injects the cells back into the patient. After three weeks, white blood cells, or lymphocytes, are removed from the area of the tumor. These modified white blood cells, believed to be the body's most potent tumor fighting agent, are duplicated in the laboratory and then injected into the patient.[21]

Gene therapy is just one of the possible applications of genetic engineering or biotechnology, the terms by which the human alteration of deoxyribonucleic acid (DNA)[22] have come to be known. Other applications of this technology range from the production of certain types of drugs to the creation of plants and animals with specific characteristics.[23] All of these applications offer great promise and benefits for mankind; yet, many observers find this new technology ethically troubling, especially when the technology is applied to human beings. One need not imagine a Brave New World or a Frankenstein to see the potential for abuse of genetic engineering. This Article will examine the process of genetic engineering, some of the ethical objections to the process, and the present system of government regulation, and will attempt to show how the governmental regulation could be improved. The focus will be on the application of genetic engineering to human beings and the specific ethical problems that arise as human beings become better able to apply this new technology to themselves. The focus is narrow and other areas, such as biotechnology in agriculture and industry, will not be addressed.[24]

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white blood cells that have migrated from other parts of the body to fight the tumor. These cells are removed from the patient and then altered in the laboratory to enable them to target and destroy the tumor. Baskerville, *supra* note 5, at 1.

19. Gina Kolata, *Cell Immunization Tested for Melanoma*, N.Y. TIMES, Oct. 9, 1991, at C14.

20. The hormone is called tumor necrosis factor (TNF). *Department of Health and Human Services, Press Release* (Oct. 8, 1991).

21. Susan Jenks, *Attempts Made to "Immunize" Patients Against Their Cancers*, J. NAT'L CANCER INST., Nov. 6, 1991, at 1532.

22. DNA is the biological molecule that determines the inherited characteristics of every living cell. *Glossary of Biotechnology Terms*, 1 HIGH TECH. LAW J. 253 (1987).

23. The drugs insulin and interferon have been genetically engineered in the laboratory; plants have been made less susceptible to the cold through genetic alteration, and animals have been created with human immune systems.

24. Industrial areas in which genetic engineering may prove useful are chemistry, energy production, and metallurgy. Bernard Talbot, *Introduction to Recombinant DNA Research, Development and Evolution of the NIH Guidelines and Proposed Legislation*, 12 U. TOL. L.R. 817 (1981).

## II. Historical Background

Man has been attempting to manipulate genetics to his advantage for centuries. Hybridization of plants, selective breeding of animals, and fermentation are all examples of simple genetic manipulation. Human beings have even altered their own gene pool through the use of conventional medicines and practiced eugenics by restricting marriages between certain people, such as first cousins.[25] What then can be so terribly troubling about modern genetic engineering? The answer to this question may be both as simple and as complex as the process of genetic manipulation itself.

The historical basis for modern genetic theory begins with Gregor Mendel's[26] work with heredity and Charles Darwin's[27] theory of natural selection.[28] The foundations of modern biotechnology were laid out in 1953 when Crick and Watson[29] described the structure of DNA. During the 1960s, researchers began investigating, or decoding, the structure of proteins such as DNA. Finally, in 1973, two scientists at Stanford University, Cohen and Boyer, developed a process for cutting sections from DNA and inserting a different piece of DNA into the gap.[30] This process, called "recombination," allowed the researchers to create new proteins. The mere account of the historical development of recombinant DNA technology belies the biological importance of this new technique, for DNA is "sometimes called the 'master molecule of life' since almost all living things — including plants, animals and bacteria — possess it."[31]

Cells form the basic components of an organism and, even though each cell has a similar structure, it performs a specific and

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25. James F. Keenan, *What is Morally New in Genetic Manipulation?*, 1 HUM. GENE THERAPY 289 (1990).

26. Mendel was a German monk who postulated the existence of genes in 1865 based on his work with the hereditary traits of peas. Scientists have recently discovered that the parent from whom a gene is inherited may be a critical factor in the occurrence of genetic disease. Such a finding is a significant exception to Mendel's theory of heredity which espoused the belief that genes were equivalent whether they were inherited from the male or female. Gina Kolata, *Biologists Stumble Across New Pattern of Inheritance*, N.Y. TIMES, July 16, 1991, at C1.

27. English naturalist, 1809-82.

28. John C. Fletcher, *Moral Problems and Ethical Issues in Prospective Human Gene Therapy*, 69 VA. L. REV. 515 (1983).

29. Francis Crick was a young American scientist who had not yet received his Ph.D., and James Watson was a twenty-four year old English scientist. The events surrounding the discovery of the structure of DNA are described by Watson in his book *Double Helix*. Judith Areen, *Regulating Human Gene Therapy*, 88 W. VA. L. REV. 153 (1985).

30. William H. Von Ochsen, *Regulating Genetic Engineering in an Era of Judicial Deference: A Proper Balance of Federal Powers*, 40 ADMIN. L.J. 303 (1988).

31. PRESIDENT'S COMMISSION ON THE ETHICAL ASPECTS OF GENETIC ENGINEERING: SPLICING LIFE, at II-1 (1983) [hereinafter SPLICING LIFE].

quite different function. In the nucleus of each cell are structures called chromosomes that store and transmit genetic information.[32] These chromosomes come in pairs,[33] and the number of chromosomes present in a cell determines whether it is a germ cell (the reproductive cells — sperm or egg — which contain only one chromosome from each pair) or a somatic cell (the body cells which contain a full complement of chromosomes).[34] Each chromosome is composed of a long strand of DNA, which in turn is "made up of chemicals called nucleotides, consisting of one small sugar molecule, one phosphate group, and one of four nitrogenous bases, which can be thought of as the four letters of the genetic alphabet (A, G, T, and C)."[35]

In the model proposed by Crick and Watson, the structure of the DNA appears as "two strings of nucleotides that are lined up next to each other like the sides of a zipper — the phosphates and sugars forming the ribbons and the nitrogenous bases acting like the interlocking teeth of the zipper."[36] The order of the nucleotide bases determines the genetic code of a particular piece of DNA and thus specifies the function of the cell.[37] In each chromosome, the genetic code is broken down into units or segments called genes.[38] Each gene contains an average of 1,000 pairs of nitrogenous bases and has the specific information to manufacture one specific protein.[39] Proteins are made up of amino acids, and amino acids, in turn, are composed of three nucleotides.[40] The President's Commission on Genetic Engineering likened this process to letters forming a word, with the nucleotides acting as the letters and the amino acid as the word.[41]

The genetic information in the nucleus is "read" and transferred to a unique messenger ribonucleic acid (mRNA) molecule, which carries the information to the cell's cytoplasm, where the

32. "Chromosome" is from Greek — "Chromo" for colored and "some" for body. SHERMAN ELIAS AND GEORGE J. ANNAS, REPRODUCTIVE GENETICS AND THE LAW (1987).

33. Humans have 46 or 23 pairs of chromosomes. Of these 23 pairs, the male and female have 22 identical sets, which are called autosomes, and one pair — the sex chromosome — that determines the sex of the individual. In females the sex chromosomes are both x chromosomes, while in the male there is one x and one y chromosome. *Id.* at 6-7.

34. *Id.*; *see also* SPLICING LIFE, *supra* note 31, at II-2.

35. Elias and Annas, *supra* note 32, at 1. A stands for adenine, T for thymine, G for guanine, and C for cytosine. Adrienne Naumann, *Federal Regulation of Recombinant DNA Technology: Time for Change*, 1 HIGH TECH. L.J. 61 (1986).

36. SPLICING LIFE, *supra* note 31, at II-3.

37. SPLICING LIFE, *supra* note 31, at II-3.

38. SPLICING LIFE, *supra* note 31, at II-3.

39. Naumann, *supra* note 35, at 62; *see also* SPLICING LIFE, *supra* note 31, at II-3.

40. SPLICING LIFE, *supra* note 31, at II-3.

41. SPLICING LIFE, *supra* note 31, at II-3.

amino acids and proteins are produced.[42] Proteins make up the structural, regulatory and metabolic elements of the cell; therefore, altering the genetic information transmitted by the RNA can have a dramatic effect on the cell.[43] Changes occasionally occur in the sequence of the nucleotide bases. These changes can be due to either the influence of an outside organism, a virus for example, or the failure of the cell to properly replicate the genetic information when it divides.[44] In either case, these changes are called mutations if they occur in the active portion of the genetic material.[45] Small mutations can be insignificant; on the other hand, even seemingly minor changes may result in disease.[46] Mutations that are passed on to future generations are called genetic diseases.[47]

Humans entered the field of internal genetic alteration in the 1970s as a result of the work of Boyer and Cohen, two researchers at Stanford University. Boyer discovered that fragments could be broken from the DNA chain and then reattached to the chain or attached to each other in different ways to create an entirely new DNA chain.[48] The resulting product is called recombinant DNA (rDNA). The key to breaking apart DNA was the discovery of restriction enzymes, substances found in bacteria that enable the bacteria to protect itself from viruses by breaking down the virus' DNA.[49] Using this cut-and-splice technique, Cohen took a piece of DNA from an African frog and inserted it into a plasmid.[50] When the plasmid divided, it replicated both the rDNA plasmid cells and

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42. Naumann, *supra* note 35, at 62-63.

43. All cells contain basically the same genetic material in their nuclei, but only a small portion of this genetic information is active. Thus, the specialized nature of the cell derives from the active portion of the genetic material in the cell. SPLICING LIFE, *supra* note 31, at II-4.

44. SPLICING LIFE, *supra* note 31, at II-4-5.

45. SPLICING LIFE, *supra* note 31, at II-4.

46. Sickle cell anemia, in which "a change in the sixth triplet of the gene for hemoglobin B-chains from CTT to CAT results in a coding for a valine instead of glutamic acid in the sixth amino acid position," is an example of a minor change that results in disease. ELIAS & ANNAS, *supra* note 32, at 6.

47. There are three simple or Mendelian patterns of inheritance for mutant genes: 1) autosomal dominant; 2) autosomal recessive; and 3) sex-linked. Regardless of the method of transfer, the incidence of many Mendelian disorders is very rare — perhaps only one per 10,000 to 50,000 births. Taken in the aggregate, however, Mendelian disorders affect about 1% of the babies born in the world and, in certain high-risk families, the chance of disease may range from 25% to 50% depending on mode of inheritance. ELIAS & ANNAS, *supra* note 32, at 25-26.

48. Von Ochsen, *supra*, note 30, at 303.

49. The number of restriction enzymes presently identified allow the breaking apart of DNA at any given sequence of nucleotides. SPLICING LIFE, *supra* note 31, at II-6, 7.

50. A plasmid is a circular, double-stranded piece of DNA found in bacteria cells that is able to divide apart from the cell's chromosomes. Von Ochsen, *supra* note 30, at 308.

the frog DNA.[51] The term for the entire process of reproducing a specific piece of DNA is called cloning.[52] Through the use of cloning on a large scale, it is possible to produce a quantity of a particular protein that is useful to research, medicine and/or industry.[53]

The beneficial application of this technology can clearly be seen in the use of recombinant DNA techniques to produce medicines. The Food and Drug Administration (FDA) has already licensed various genetically engineered drugs, including "a vaccine against hepatitis B, a kind of monoclonal antibody that increases the success of kidney transplants, an enzyme that dissolves blood clots, gene-spliced human insulin, and a class of proteins, called interferons, that regulate the response of cells to viral infections and cancer proliferation."[54] But, as the recently begun human gene therapy trials clearly demonstrate, genetic engineering has far greater medical potential than the mere production of drugs.

The term gene therapy is used to describe the introduction of a normally functioning gene into a human suffering from a genetic defect or disease in an attempt to cure the defect or disease.[55] The application of this therapy can take place in either the somatic cells or the germ cells of the patient. The key difference between these two types of gene therapy is that alterations to the somatic cells will affect only the patient in question, while gene therapy to correct a defect in the germ cells will pass on the corrected gene to future generations.[56] Both of the trials presently being conducted in humans employ somatic cell gene therapy and, to date, there have been no attempts to use germ cell therapy in humans.[57] Even so, the possibility of altering future generations' genetic make-up has concerned some ethicists and theologians. In addition, as human beings become more advanced in the application of biotechnology, the possibility of

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51. Von Ochsen, *supra* note 30, at 308.

52. Naumann, *supra* note 35, at 63.

53. Robert F. Baker and Wendy G. Clough, *The Technical Uses and Methodology of Recombinant DNA*, 51 S. CAL. L. REV. 1009 (1978).

54. Von Ochsen, *supra* note 30, at 310. Genetic engineering of monoclonal antibodies has received considerable attention in recent months. In February, the *New York Times* reported on a study appearing in *The New England Journal of Medicine* on the use of monoclonal antibodies to combat the effects of septic shock. Natalie Angier, *Drug Cuts Deaths Tied to Infection*, N.Y. TIMES, Feb. 13, 1991, at A1. For a more general discussion of genetically engineered monoclonal antibodies, *see* Lawrence M. Fisher, *Biologists Re-Engineer Antibodies*, N.Y. TIMES, Mar. 5, 1991, at C1.

55. SPLICING LIFE, *supra* note 31, at II-16.

56. SPLICING LIFE, *supra* note 31, at II-16-20.

57. Experiments using germ-line therapy have been performed in animals, but the general opinion in the scientific community is that any human application is, at present, only a very distant possibility.

enhancement genetic engineering[58] and eugenic genetic engineering[59] become more real. Thus, we are at the very beginning of the direct application of genetic manipulation to human beings — the point where the line between science and technology begins to blur. This is also the point at which human beings should re-evaluate the relationships among the science/technology of genetic manipulation, the ethical problems created by the application of the technology to humans, and the law regulating genetic manipulation before moving on to the next level of human gene therapy.

## III. Ethical Concerns

Any analysis of the ethical concerns raised by genetic engineering must begin with the very basic but highly complex concept of what is "human" and how the greater understanding of the processes that make us function affects our concept of humanity. There can be no question that "[b]iology, including genetics, is particularly important because it is the science . . . [that] . . . speaks to the fundamental nature of human beings."[60] The genetic code is the blueprint that determines how each human life is to proceed. As we learn more about the present and potential powers of genetic engineering, we cannot help but think more about the nature, meaning, and value of human life.[61] Thus, it is little wonder that:

> [T]he deepest source of our uneasiness about genetic engineering lies in a pervasive sense that there is something sacred about the remarkable process by which the order and intelligibility proper to all life are literally given flesh in the genetic code, and therefore, there is something impious about manipulating genetic material.[62]

This basic argument is advanced both by theologians, who believe that the genetic code is God's work and that humans who attempt to manipulate genetics are trespassing on God's domain, and by secular

58. Enhancement genetic engineering is the process of inserting a gene into a person in an attempt to enhance a specific physical characteristic; for example, adding genes for growth in an attempt to produce a tall individual. ELIAS & ANNAS, *supra* note 32, at 267.

59. Eugenic genetic engineering is the attempt to alter or improve complex human traits that are at least partially genetic in origin, *i.e.*, intelligence, athletic ability, or personality. ELIAS & ANNAS, *supra* note 32, at 267.

60. Maxine F. Singer, *Genetics and the Law: A Scientist's View*, 3 YALE L. & POL'Y REV. 315, 318 (1985).

61. J. Robert Nelson, *The Human Problem of Human Genetic Engineering*, in GENETICS AND THE LAW III 82 (1985).

62. Jean Porter, *What Is Morally Distinctive About Genetic Engineering*, 1 HUM. GENE THERAPY 419, 420 (1990).

theorists, who feel that the genetic code is what makes us human and that any attempt to alter the code would begin a process that could make us less human.[63] In either instance, the basis for judging the advisability of genetic engineering is a predetermined set of moral principles or rules of conduct. Ethical decisions that are based on pre-existing moral principles are termed *a priori*.[64] Under a system of *a priori* ethics, those things that are wrong have always been and are always wrong. No matter what the situation, the "inherent wrongness was believed by faith and by metaphysical opinion to be a matter of 'natural' moral law or divine revelation."[65] Thus, to interfere with the human genetic code, even if the interference was for a legitimate purpose, would violate an *a priori* scheme of ethics and would be held to be against natural moral law.

The moral certainty with which one may act under an *a priori* ethical system holds definite appeal. After all, who would not say that they stood for the sanctity of the very thing that makes us human. Yet to dismiss genetic engineering as unnatural without considering the potential benefits of the process seems harsh. This is especially true when we consider that:

> At various times, equality of rights, slavery, the subordination of women, vegetarianism, and animal husbandry have all been defended as natural; homosexuality, the accrual of interest on a sum of money, intensive agriculture, the use of cosmetics and the use of anesthetics in childbirth have all been condemned as unnatural.[66]

In each case, opinions of what is morally natural have changed as a result of a case-by-case analysis of the merits of each action. In addition, both philosophers and scientists agree that it is incorrect to define humanness solely on the properties of DNA.[67] The genetic code is necessary to human existence, but factors such as society and culture also play an important role in defining what is considered to be human. Therefore, "[s]ince societies and cultures change, as well as differ from each other, certain elements in the concept of humanness are variable, and there is no generally agreed upon definition of

63. Carol A. Tauer, *Does Human Gene Therapy Raise New Ethical Questions?*, 1 HUM. GENE THERAPY 411 (1990).

64. Joseph Fletcher, *Ethical Aspects of Genetic Controls: Designed Changes in Man*, 285 NEW ENG. J. MED. 777 (1971).

65. *Id.* at 778.

66. Porter, *supra* note 62, at 420.

67. Singer, *supra* note 60, at 325-28; *see also* Fletcher, *supra* note 64, at 781.

what 'humanness' requires."[68] The *a priori* argument against human genetic engineering must fail because, while the genetic code is worthy of awe and respect, it is not the thing that defines the natural moral law of being human. Whether human actions are natural "in a normative sense, is defined by what is characteristic of human life as a whole, namely, our capacities for intelligent self-direction, and not by the biological processes that sustain our life, but do not give it its characteristic shape."[69]

How, then, should we determine whether the advance of genetic manipulation in humans is ethical if we do not use the *a priori* system? Once again, we are faced by the difficult task of attempting to define what is human. The task is made even more difficult when we discover that some who have considered the problem have concluded, "[T]he fact is that most of our discourse about the ethics of biomedical innovation is a semantic swamp, because what we mean by 'human' and ergo by 'humanistic' usually remains vague and poorly defined."[70]

The most logical way out of the swamp appears to be that provided by the school of "virtue ethics."[71] Under this approach, the agent and the action are seen as one and analyzed according to their effect on humans and human society.[72] Thus, the key question to be asked in determining if conduct is ethical is not whether we have a right to act, but, rather, what we become if we act.[73] Therefore, unlike *a priori* ethics, consequences are factored into the ethical equation, and the merits of each case determine whether an action is ethical.

Both religious and secular groups are able to agree on the basic concept of the sanctity of human life. Listed among the fundamental elements required by this concept are "a basic respect for human beings, for their civil rights, their personal rights to the care and defense of their bodies and minds, and their proxy rights for depen-

68. Tauer, *supra* note 63, at 413.

69. Porter, *supra* note 62, at 422.

70. Fletcher, *supra* note 64, at 781. Fletcher goes on to suggest that it is far past the time when a definition acceptable to medical, ethical, and legal communities should have been established, and he urges swift action to find a non-doctrinal solution to this problem as quickly as possible. Regrettably, since the time that this article was published in 1971, there has been little progress toward any working definition of what it is to be human.

71. Keenan, *supra* note 25, at 289.

72. Keenan, *supra* note 25, at 289.

73. Keenan phrases the question in a slightly different way, but with the same result. First, he says we must ask who are we, then who we should become and, finally, how we get there. If an action does not move us toward the type of beings that we should become, it is not ethical. Kennan, *supra* note 25, at 289.

dent relatives who are either small children or incompetent."[74] These fundamental rights[75] — the sanctity of life — form the basis for both medical ethics in general and, more specifically, the ethics of genetic manipulation. Thus, human beings are seen as subjects possessing the rights that are fundamental to the concept of the sanctity of life. When we consider any act and the consequences of that act, we must determine to what extent the act diminishes the sanctity of life or, put another way, how much an act transforms a human into an object.[76] Thus, we see an act as morally wrong when it objectifies a human being, and, "[i]n fact, the enduring critique of medical work has been whenever the person is not treated as a person but as a body or an object."[77]

Presented with the virtue ethics question of what we become if we act, we must then stay clear of actions that make human beings objects and pursue the courses that give greater meaning to the sanctity of life. In the context of modern medicine, where developing new therapies is a trial-and-error process, the overriding concern of the physician is to do no harm to the patient[78] and, in areas that are untried, to proceed with caution.[79] In this light, we can clearly see that "[t]he ethical grounds from which the argument for human gene therapy arises are imperatives to relieve human suffering, prevent premature death, and remove life-long burdens among the heaviest that persons must bear."[80] At this point we must begin to distinguish among the four categories of genetic manipulation (somatic cell therapy, germ-line therapy, enhancement genetic engineering, and eugenic genetic engineering), because the potential for dehu-

74. Nelson, *supra* note 61, at 83.

75. Dr. Fletcher takes issue with the use of the term "rights" to describe the controlling factor in the test for ethical behavior. He prefers to think of human needs as the factor on which the test hinges. Under Fletcher's approach, "[r]ights are nothing but a formal recognition by society of certain human needs, and as needs change with the changing conditions of society so rights should change too." Despite the difference in terminology, the thrust of Fletcher's test for the ethical acceptability of a medical process using genetics is also the reduction of human suffering. Fletcher, *supra* note 64, at 782.

76. Any act that treats a human being as an object has always been perceived as immoral because such acts are generally acts of oppression. Slavery is a classic example of an act of oppression that creates objects of human beings. Keenan, *supra* note 25, at 293.

77. Keenan, *supra* note 25, at 292.

78. Dr. W. French Anderson endorses this approach in an editorial he wrote prior to the first human trials using somatic cell gene therapy. W. French Anderson, *What's the Rush?*, 1 HUM. GENE THERAPY 109 (1990). This sentiment is also embodied in the moral motto of medicine: *Primum non nocere* — first of all, do no harm. Nelson, *supra* note 61, at 83-84.

79. Nelson, *supra* note 61, at 83-84.

80. John C. Fletcher, *Controversies in Research Ethics Affecting the Future of Human Gene Therapy*, 1 HUM. GENE THERAPY 307 (1990).

manization increases with each step.[81]

The first level of genetic manipulation is somatic cell gene therapy, which as we have discussed, involves the alteration of body cells in the attempt to cure an existing genetic defect. This type of gene therapy affects only the recipient of the genetically altered material and cannot be passed on to future generations.[82] Thus, on the surface there seems to be only one major difference between somatic cell gene therapy and conventional medicine: Conventional medicine attacks the source of the disease. For those who favor an *a priori* ethical system, this presents considerable problems. We must remember, however, that "DNA within cells is not inviolate; for example, within the DNA of many organisms is found DNA from separate entities, viruses, which inserted itself either generations ago or during a recent infection."[83] In addition, the structure of DNA is not fixed; rather, it changes through natural mutation or by shuffling, repeating and/or deleting pieces. Throughout the "[a]ddition or subtraction of a single segment of DNA, whether as a result of an entirely natural process or as a result of genetic engineering, does not make a significant difference to the identity of the organism."[84]

Applying the ethical framework that we have developed, the process of somatic cell gene therapy is no more objectionable than the use of modern medicine, for both seek to relieve human suffering.[85] Therefore, when physicians employ somatic cell gene therapy to combat diseases such as ADA or melanoma, we become a species that is more concerned with the sanctity and preservation of life.

The ethical propriety of gene therapy becomes somewhat more complex when we move from the consideration of somatic cell therapy to the use of germ-line gene therapy. Germ-line therapy is conducted in the germ cells or gametes, the cells that are designed for reproduction of the species.[86] Genetic alterations in these cells would prevent a defect from being inherited by future generations and thus would affect the content of the human genetic pool.[87] There has been no attempt to use germ-line therapy in humans to date, but experi-

81. Keenan, *supra* note 25, at 289.

82. SPLICING LIFE, *supra* note 31, at II-20.

83. Singer, *supra* note 60, at 328.

84. Singer, *supra* note 60, at 325.

85. Generally speaking, the view of the scientific community is that somatic cell gene therapy does not differ substantially from organ transplants or bone marrow injections. Judith Areen and Patricia King, *Legal Regulation of Human Gene Therapy*, 1 HUM. GENE THERAPY 151 (1990).

86. Singer, *supra* note 60, at 329.

87. Singer, *supra* note 60, at 329.

ments in animals have shown that the transmission of altered genetic material from one generation to another is possible even though the success rate has been low.[88]

Two techniques currently being used on laboratory animals could be used to alter human germ cells. First, given that the human male produces sperm cells continuously from puberty until death, the alteration of the cells could take place in the adult male. This approach may not be feasible because it is very difficult to target the specific cells to be altered.[89] The second possible method of altering germ cells is to genetically modify embryonic cells before they begin to differentiate.[90] If this were done, all the cells of the developing fetus, including the germ cells, would be affected by the modification.[91] This method of "germ-line genetic modification is more advanced scientifically, . . . [however,] it is ethically and politically more controversial because it requires the manipulation of early human embryos."[92] Thus, germ-line gene therapy presents us with several levels of ethical problems: Is the alteration of future generations who cannot speak for themselves ethical and, if so, how should the genetic alteration take place?

One of the first concerns of those who question the advisability of germ-line therapy is the effect of the therapy on the human genetic pool. In the long run, the argument goes, the elimination of what we believe to be harmful genes from the human gene pool will reduce the species' ability to adapt to changing environmental conditions and thus reduce the chance of overall survival. Put another way, the proponents of this theory would answer the question of "what would we become if we conduct germ-line gene therapy" by saying that we would become less likely to survive as a species. Under the virtue ethics system, any action that would reduce the chance of survival of the species would quite probably be seen as unethical. However, this objection to germ-line therapy fails to consider two important factors. First, the fact that the gene has been removed by genetic manipulation does not mean that it could not be reintroduced by the same process if it were discovered that the gene served a beneficial purpose.

> If we could engineer away the 'defects,' we could presumably engineer them back were we to discover that they had a desira-

88. Tauer, *supra* note 63, at 413.
89. Tauer, *supra* note 63, at 415.
90. Tauer, *supra* note 63, at 415.
91. SPLICING LIFE, *supra* note 31, at II-20-21; *see also* Tauer, *supra* note 63, at 415.
92. Tauer, *supra* note 63, at 415.

> ble side effect (unless one generation were to take the unlikely step of engineering into the next generation an aversion to genetic engineering or the inability to engage in it).[93]

Second, while there is no doubt that certain genes will be eliminated from the gene pool, there is no assurance that other genes will not be introduced. Therefore, rather than being restricted, the human gene pool may be expanded, and human beings will become more, as opposed to less, adaptable to ecological changes.

In addition, this ecological argument against germ-line therapy seems to assume that the natural production of genes is the key to evolution. This, however, is not the case. Nature does not plan evolution by the production of genes; rather, evolution occurs by random choice through the process of natural selection.[94] Human intervention in the selection process merely imposes a plan on the system and to some "[i]t makes more sense to plan for the future event with imperfect information, than to sit idly by waiting for the genetic roulette wheel to stop spinning."[95]

In this light, what initially appeared to fail the virtue ethics test for ethical action now seems to be in the best interest of society. Through the practice of germ-line therapy, we would become more concerned with both the life of those affected by the genetic disorder and the life of the species. Even so, there is a long-standing ethical aversion to performing medical procedures on persons without their consent. The future generations who will be affected by germ-line therapy are not in a position to consent to treatment, but their parents may legally consent for them. In addition, we may test the ethics of an action by placing ourselves in the position of the future generations. If we were able to conduct germ-line gene therapy but did not, the future generations affected by the genetic disease would be harmed.[96] This, of course, would violate the medical principle that no harm should result from the practice of medicine. Thus, even without consent, the application of germ-line gene therapy satisfies the virtue ethics test for ethical action.

E. Joshua Rosenkrantz, a former law clerk to Justice William

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93. E. Joshua Rosenkrantz, *Custom Kids and the Moral Duty to Genetically Engineer Our Children*, 2 HIGH TECH. L.J. 1, 23 (1987).

94. *Id.* at 24.

95. *Id.* In addition, the author points out that another problem presented by this argument is that human beings have already altered the gene pool through the use of modern medicine. Thus, the internal human manipulation of germ cells may only be a balance to what has come before. *Id.*

96. Fletcher, *supra* note 28, at 542-43.

Brennan,[97] places a different emphasis on the use of genetic manipulation when the process is to be applied to children and future generations. In this context, he argues that a parent has a moral duty to genetically rescue a child from the suffering of a genetic disease.[98] This duty derives from the fact that, "If a prenatal diagnosis shows that a fetus has a serious single-cell defect and the mother opposes abortion, prenatal treatment may be essential to prevent the damage that will occur when a gene necessary for normal development is missing."[99] Thus, the duty would apply to both germ-line and somatic cell therapy.

Under Rosenkrantz's theory, a rescue is defined as an act that is beneficial to the rescued and that does not change the identity of the person who is rescued.[100] In the case of genetic engineering, it is clear that the alleviation of suffering caused by genetic disease would certainly be beneficial to a person afflicted with such a disease. In addition, the identity of an individual, like the definition of what is human, is not dependent on genes alone. Yet, even if genetics were the sole determiner of an individual's identity, "[m]ost people do not understand that in most cases manipulation of DNA results in only a very small change in the genetic make-up of an organism."[101] Thus, from a strictly scientific point of view, the individual's identity is not changed by genetic manipulation. Rosenkrantz answers the identity question in a slightly more humanistic fashion by applying a rule of "closest continuation."[102] Under this theory, if the person being rescued is causally dependent on the person doing the rescuing and the rescued person is in the closest relationship to the person rescuing him, then the identity of the person before and after the rescue is the same. Put in a simpler fashion, "[o]ur identity analysis boils down to no more than a comparison of the person that the egg would have produced (but for the intervention) to the person that it will produce (after the intervention)."[103]

When this test is applied to either possible technique for germline gene therapy, we see that both prongs are satisfied. The post-

97. Mr. Rosenkrantz was clerk to Justice Brennan during the 1987-88 term of the Supreme Court.

98. Rosenkrantz, *supra* note 93.

99. John A. Robertson, *Genetic Alteration of Embryos: The Ethical Issues*, in GENETICS AND THE LAW III 118 (1985).

100. Rosenkrantz, *supra* note 93, at 25-27, 38.

101. Singer, *supra* note 60, at 325.

102. Rosenkrantz, *supra* note 93, at 27-28. The closest continuation theory applied by the author is the work of the philosopher Robert Nozick.

103. Rosenkrantz, *supra* note 93, at 41.

genetic manipulation child is: (1) causally dependent on; and (2) in the closest relationship to the pre-gene therapy sperm cell or embryo — the only real difference between the two being the absence of the genetic defect. Therefore, according to Rosenkrantz, not only is it ethical to conduct germ-line gene therapy, but it is also the duty of a parent to use gene therapy to rescue a child from the suffering caused by genetic disease.[104]

Of course, there must be limits to the moral duty of a parent to perform a genetic rescue. The easiest and most understandable limit on such a duty would parallel the limits on a parent's moral duty to aid a child in other ways. The most obvious parallel to the genetic rescue is the duty to provide conventional medical care when a child is ill. Using this principle as a guideline, Rosenkrantz creates a "parallel cure" theory, under which "parents must rescue their child genetically (all else being equal) to the extent that they would be morally bound to cure or compensate for a child's trait conventionally, once it manifests itself."[105]

Now that we have established that the overall concept of germ-line therapy is ethical under the virtue ethics system, we must move to the second level of ethical questions and determine if it is ethical to pursue germ-line gene therapy using either of the techniques currently being investigated. There seems to be very few ethical problems with the technique of altering the cells that produce sperm in the adult male because an adult could consent to the process. As we have discussed, however, this process is the more problematic of the two techniques. Therefore, we must turn our attention to the ethical considerations of genetic manipulation in the pre-differentiated human embryo.

To begin with, the possibility of human germ-line therapy is, at present, many years away.[106] Yet the steps leading to human trials with germ-line therapy require considerable ethical analysis because much of the research involved will require the use of human embryos.[107] It is important to note that "[i]n contrast to an ethos of deep approval for somatic cell therapy, the moral climate surrounding . . . [research on in utero and ex utero human fetuses, and re-

104. Rosenkrantz, *supra* note 93, at 38-44.

105. Rosenkrantz, *supra* note 93, at 46.

106. Writing in 1983, Fletcher placed the potential date for the use of germ-line therapy at 50 to 100 years in the future or well after somatic cell therapy has become highly successful. Fletcher, *supra* note 28, at 534. Even if Dr. Fletcher's prediction should be revised in the wake of the first human trials with somatic cell therapy, the advent of human use of germ-line therapy is still in the distant future.

107. Fletcher, *supra* note 80, at 307, 311-21; *see also* Tauer, *supra* note 63, at 415-16.

search using in vitro fertilization] is in a stage of polarization and paralysis of action, especially in the federal sector of U.S. science."[108]

The federal government is not the only area in which these topics elicit a polarized response. Religious groups, particularly the Roman Catholic church, have condemned the practices of in vitro fertilization and fetal experimentation.[109] In short, the religious argument against in vitro fertilization is that it removes the unity of husband and wife from procreation and dehumanizes procreation and parenthood.[110] The Church's opposition to fetal research is also well known. In short, the Church's opinion is based on the belief that life begins at conception and that any harm or destruction to early human embryos is an immoral act.[111]

From a logical point of view, the position of the Catholic Church on this issue is undermined to some degree by the Church's inconsistent stand on the human application of gene therapy."[112] The Vatican has approved the use of somatic cell gene therapy after birth in cases of persons suffering from serious diseases.[113] Yet, the Church steadfastly refuses to endorse the use of such therapy prior to birth. However, this position appears to contrast the Catholic belief that the fetus is just as much a person before and after birth.[114] The Catholic Church appears to be caught in the awkward position of saying that fetuses are entitled to all the rights of an adult (including the ability to use somatic cell gene therapy),[115] but that any adult who tries to develop direct medical care for the fetus (a process that must involve human research to determine safety and efficacy), in the hope of reducing the suffering after birth, is committing an

108. Fletcher, *supra* note 80, at 309.

109. Richard A. McCormick, HOW BRAVE A NEW WORLD? 303, 312-17 (1981); *see also* LeRoy Walters, *Ethical Issues in Human In Vitro Fertilization and Embryo Transfers*, in GENETICS AND THE LAW III 215 (1985).

110. For a more in-depth discussion of the religious objections to genetic alteration and in vitro fertilization, *see* Paul Ramsey, *Fabricated Man: The Ethics Of Genetic Control* (1977).

111. Keenan, *supra* note 25, at 295. For a general discussion of various religious attitudes in this topic, *see* McCormick, *supra* note 109, at 281-335.

112. Some Catholic philosophers have argued that the traditional Catholic values do not support a certain and complete moral objection to any conduct affecting early human embryos. In addition, the Church's own official statements, on occasion, have noted that there is disagreement over the moral questions concerning early human embryos. Tauer, *supra* note 63, at 416.

113. Rosenkrantz, *supra* note 93, at 35 n.142.

114. Rosenkrantz, *supra* note 93, at 35-36.

115. Somatic cell therapy in a fetus essentially results in germ-line therapy since, at the time of the manipulation, the fetus is undifferentiated. When the fetus' cells begin to differentiate, the cells will all carry the newly inserted genes. Tauer, *supra* note 63, at 416.

immoral act.

This is a perfect example of why the *a priori* ethical approach is ill-suited for the analysis of scientific developments. Therefore, we shall apply the virtue ethics analysis to in vitro fertilization and the research necessary for the development of germ-line gene therapy. What, then, do we become if we carry out the process of in vitro fertilization and fetal research? Once again, we must look at the characteristics that make us human. We begin the analysis by noticing that "[m]an is a maker and a selector and a designer, and the more rationally contrived and deliberate anything is, the more human it is."[116] Thus, it seems that in vitro fertilization is a very human process because it is rational and carefully planned. In addition, the ability to reduce suffering and eliminate genetic disorders through the use of genetic manipulation and in vitro fertilization creates a possible benefit to all human beings. Surely we cannot believe that it is debasing our humanness to accomplish, through rational planning, a world with less human suffering. On the contrary, it seems that "human life would be debased if we could easily do something fundamentally to improve that life but refrained from doing so."[117] Therefore, it appears that using in vitro fertilization to develop the process of germ-line gene therapy makes us more, and not less, human.

There is, however, one gnawing ethical problem hidden in the otherwise bright picture just painted: the ethical considerations of fetal research. These considerations boil down to the question of when, if ever, is it proper to develop human embryos for in vitro research. The answers to this question, as one might expect, are varied. In Great Britain, research is allowed on human fetuses for up to fourteen days after fertilization;[118] however, in West Germany, the Bundestag condemned all genetic research on embryos and recommended that it be a federal criminal offense to attempt to bring to term an embryo that had been genetically manipulated.[119] The United States has taken a different approach to the problem. In 1975 a moratorium on research using in vitro fertilization was declared, and the Department of Health and Human Services (DHHS) appointed an Ethical Advisory Board (EAB) to study the matter.

116. Fletcher, *supra* note 64, at 780.

117. Rosenkrantz, *supra* note 93, at 35.

118. The House of Commons voted on the matter on April 23, 1990, and by a vote of 364-193 approved the use of fetal research. Tauer, *supra* note 63, at 415.

119. Tauer, *supra* note 63, at 415.

The EAB approved the limited use of embryo research,[120] but DHHS never implemented the proposal.[121] Thus, the moratorium on federal funding for in vitro embryo research continues to be in effect.[122] In vitro embryo research may be conducted by using private funds if not prohibited by state law; however, some commentators feel that the federal research ban discourages and inhibits private research.[123]

In vitro research on the human embryo, or, more precisely, the pre-embryo, is important to the development of human gene therapy because, before germ-line gene therapy can begin, scientists must study the development of the human zygote[124] to determine how genetic diseases begin and function. In addition, researchers must determine whether the process of germ-line therapy actually does prevent the inheritance of genetic diseases in humans. Therefore, if the potential benefits of human germ-line gene therapy are to be realized in the United States, we must as a society determine whether it is ethical to use human pre-embryos in research. The present paralysis or procrastination being practiced by the federal government is clearly unacceptable. This is not meant to belittle the government, for this is a truly difficult question, but other governments have

120. The EAB laid out six criteria that would have to be met if research using human zygotes was to be ethical: 1) research must comply with existing guidelines for human experimentation; 2) research must be designed primarily to establish the safety and efficacy of transferring genes to the zygote, thus focusing on the life of the zygote; 3) the scientific merit of the study must be exceptional and the results obtainable only through the use of human embryos; 4) germ cells should be obtained only from informed and voluntary donors; 5) no embryo should be allowed to develop past 14 days after fertilization — the normal time for implantation; and 6) researchers should promptly report any greater than normal risk of abnormalities from the use of the process. Fletcher, *supra* note 28, at 535-36.

121. Tauer, *supra* note 63, at 416. The EAB was allowed to lapse in 1979, and DHHS has not attempted to restore the EAB. Fletcher, *supra* note 64, at 309.

122. The 1975 moratorium affects all research involving in vitro fertilization and is different from a moratorium imposed by the NIH in 1989 on fetal tissue transplantation research. In addition, federal funds are available for fetal tissue research when the product of the research is not transplanted into a patient. Fletcher, *supra* note 80, at 311-16.

On July 25, 1991, the United States House of Representatives voted 274 to 144 to overturn the ban on fetal tissue research. The bill voted on by the House would cover areas that are addressed by both the 1975 and 1989 moratoriums. Despite the House vote, it was widely expected that President Bush would veto the bill. Gwen Ifill, *House Approves Fetal Tissue Use in Federally Financed Research*, N.Y. TIMES, July 26, 1991, at A11. A similar bill was approved by the Senate Labor and Human Resources Committee on February 6, 1992. David Brown and Guy Gugliotta, *On Capitol Hill—Fetal Tissue Research Backed*, WASH. POST, Feb. 6, 1992, at A11.

123. Fletcher, *supra* note 80, at 310.

124. A zygote is the cell that results from the union of a male and a female gamete until it begins to divide. DORLAND'S ILLUSTRATED MEDICAL DICTIONARY (26th ed. 1981). The developing life technically is a pre-embryo between the first cell division and the second week of development, at which time it becomes an embryo.

reached a decision on the matter and so, too, must ours.[125]

Once again, we must begin our ethical analysis by looking at the merits of the case and the consequences of our actions and answering the question of what we become if we proceed with fetal research. If in vitro embryo research is used to advance gene therapy techniques, as with somatic cell gene therapy, the ultimate merits of the case are quite strong. If the technique can be perfected, human suffering can be reduced. Thus, the ends for which the initial experimentation are being conducted will lead us to something that is desirable. This, however, is not the end of the inquiry because, to achieve these ends, scientists must fertilize human eggs in vitro for the sole purpose of using these zygotes for experiments.

If the products of these experiments were then implanted in a womb and brought to term, the resulting children might suffer as much or more than if they were born with the genetic defect that the experiment seeks to cure. Therefore, conducting these experiments would create suffering, which is clearly not a desired end. With this in mind, it appears that the dividing line between ethical experimentation and unethical experimentation should be drawn at the implantation of the zygote into the uterus. This approach is similar to the one taken by the EAB and Great Britain, both of which allow research on an embryo up to fourteen days after fertilization if good cause is established.[126]

In allowing research on zygotes only up to the point at which they may begin to develop sentience,[127] and following the other criteria laid out by the EAB, we are able to show respect for the moral status of the zygote while at the same time, we distinguish the moral standing of the zygote from that of the fetus.[128] Yet, even if the moral standing of the zygote is protected, there still remains the problem that research of this nature treats the zygote — a potential

125. It could be argued that the federal government has made a decision by its failure to act, but this would be a decision by default. What is needed to resolve this difficult problem is a decision based on an active assessment of the situation.

126. Robertson, *supra*, note 99, at 119. The 14 day period is established because, at or about 14 days after fertilization, the nervous system begins to differentiate and the possibility of sentience arises. Robertson, *supra* note 99, at 119.

127. As mentioned in note 126, 14 days after fertilization the nervous system begins to differentiate and sentience starts to develop. Robertson, *supra* note 99, at 119. This is the point by which implantation normally must be completed. Thus, it is also the point at which experimentation must stop. Fletcher, *supra* note 28, at 536.

128. The zygote is unable to fully develop without the positive step of implantation. At the point the zygote is implanted in a womb, it becomes a potential fetus. Fletcher, *supra* note 28, at 536. *Dorland's Medical Dictionary* defines a fetus as unborn offspring in the period of post embryonic development. Embryonic development is the period from two to eight weeks after fertilization. DORLAND'S MEDICAL DICTIONARY 493 (26th ed. 1981).

human — as an object. Unlike other acts that make human beings objects, however, here we are dealing with an act that is not designed to be oppressive. Thus, research that treats human zygotes as objects may still be ethical if it is conducted to reduce human suffering rather than conducted for oppressive purposes. We must be alert, however, for if this type of research was used for oppressive ends, the result would be far more devastating than any previous act that treated human beings as objects.[129]

In light of this observation, it is clear that the enhancement of specific traits and the eugenic improvement of the species are applications of genetic manipulation that, at present, are not ethical because they are based on the concept that some human beings are more valuable than others. This sort of value determination results in the treatment of human beings as objects for an immoral purpose, and, unlike the previous forms of oppression, those oppressed by eugenics would not have the opportunity to resist.[130] Therefore, if we as a species were to practice enhancement or eugenic genetic manipulation, we would become oppressors to all those people who did not possess those traits on which we placed greater value.

The position that genetic manipulation for enhancement or eugenics is not ethically advisable is backed, to some degree, by popular opinion. A public opinion poll taken by Louis Harris under the auspices of the Office of Technology Assessment in 1986 showed that 53% of the 1,273 adults who responded were against the use of genetic manipulation for enhancement.[131] On the other hand, 62% of those surveyed approved of the use of germ-line gene therapy to cure fatal genetic diseases.[132] Thus, both ethical considerations and, to a lesser degree, popular perception favor the use of gene therapy for the purpose of combating diseases and object to its application for enhancement or eugenic purposes.

## IV. The Need for Regulation

Some authors, Professor Sheldon Krimsky[133] in particular, point out that an ethical boundary for genetic manipulation based on the

129. Keenan, *supra* note 25, at 293.

130. Keenan, *supra* note 25, at 293.

131. Sheldon Krimsky, *Human Gene Therapy: Must We Know Where to Stop Before We Begin?*, 1 HUM. GENE THERAPY 171 (1990). Other results from this poll indicate that only 18% of those surveyed strongly approved of improving intelligence levels through the use of genetic manipulation and only 16% favored the improvement of athletic ability. Fletcher, *supra* note 80, at 308.

132. Krimsky, *supra* note 131, at 173.

133. Department of Urban and Environmental Policy, Tufts University, Boston, MA.

distinction between curing disease and enhancing traits rests on nebulous scientific grounds because the definition of disease is in a constant state of flux. Yet, this may be precisely why an ethical principle for genetic engineering should be based on such a distinction: It is able to change with the perceptions and needs of society. Science can be seen in any of three ways or a combination of the three. First, science may be seen as the search for truth in the natural world. Second, it may be seen as a particular method of inquiry — the scientific method. Third, it may be seen as a human enterprise dedicated to the betterment of human beings.[134] There can be no doubt that "[s]cience is now a public and social enterprise not only because much of its financial support comes from the public but just as importantly because the implications and impact of science are public and social."[135] This is especially true for genetic engineering. Therefore, it is argued that because of the public and social implications and impact of science, particularly genetic manipulation, government regulation of science is necessary.

Many scientists, however, feel that the best science is that which is conducted without social constraint. To this end "[m]any scientists claim . . . [that] they have a right of free inquiry — a right to research — that governmental constraints on scientists' choice of research topics and methods violates."[136] Thus, the idea that science is an enterprise devoted to the betterment of human beings creates a tension between the good of society and the freedom to research.[137] There must, of course, be limits imposed on any freedom when the exercise of that freedom will harm the health, safety, and welfare of others. Therefore, the state may regulate research because society may be harmed by either the research process itself or the product of the research.[138] In addition, it must be realized that the interests of the public and the interests of scientists will not always be the same. Therefore, we must concede that "[s]cientists cannot

134. Daniel Callahan, *Ethical Issues in the Control of Science*, in GENETICS AND THE LAW II 19 (1980).

135. *Id.* at 21.

136. John A. Robertson, *The Scientist's Right to Research and the Legitimacy of Governmental Regulations*, in GENETICS AND THE LAW II 29 (1980). Many times this argument is phrased in the context of the First Amendment as part of a growing movement to recognize a right to gather information. If such a constitutional right to research exists, then government could only regulate scientific research by establishing a compelling state interest. *Id.* at 29-30.

137. Callahan, *supra* note 134, at 20.

138. Robertson, *supra* note 136, at 30. In either case, the government is regulating the process by which the research is conducted, in one case by saying how it is to be carried out and in the other by saying that it cannot be carried out because of the harm produced by the end-product. In terms of the First Amendment, these types of regulations fall under the heading of time, place and manner restrictions. Robertson, *supra* note 136, at 32.

fully regulate themselves in the public interest because they are not necessarily representative of the public."[139] Despite the initial success of self-regulation by scientists in the field of genetic engineering,[140] the need for outside regulation is apparent due to the severe consequences that could arise if the process was abused.

Even with a system of governmental regulation, some scientists will attempt to avoid the established protocol and conduct research as they please. This is clearly shown by the incident in 1980 involving UCLA researcher Martin Cline. Dr. Cline "will go down in medical history as the first person to attempt to transplant cloned genes into human patients, his particular purpose being to effect a cure for the dreaded globin disease beta thalassemia."[141] Dr. Cline performed the experiments in Italy and Israel, but failed to receive approval from either government or from the necessary review boards at UCLA.[142]

When the violations were reported, the National Institute of Health (NIH) conducted a review of the matter. The NIH concluded that Dr. Cline was in violation of the established procedure and removed federal funding from Dr. Cline's projects.[143] In a more

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139. Callahan, *supra* note 134, at 24. The position that scientists should not be allowed to regulate themselves has been advanced by many prominent members of the legal community, including Judge David Bazelon of the District of Columbia Court of Appeals and Senator Albert Gore. David Bazelon, *Coping With Technology Through the Legal Process*, 62 CORNELL L. REV. 817 (1977); Senator Albert Gore and Steve Owens, *The Challenge of Biotechnology*, 3 YALE L. & POL'Y REV. 336 (1985); Senator Albert Gore, *A Congressional Perspective*, in BIOTECHNOLOGY IMPLICATIONS FOR PUBLIC POLICY, THE BROOKINGS INSTITUTE (1985).

140. In 1974, the National Academy of Science (NAS) called together a group of concerned scientists to discuss the potential hazards presented by genetic engineering experiments. The committee proposed a worldwide moratorium on certain high-risk experiments and called on the NIH to create an advisory body to oversee the development of rDNA processes. In addition, the committee called for an international conference on rDNA. The conference was held at the Asilomar Conference Center in Palo Alto, California in February 1975 and was attended by representatives of 150 countries. During the seven months between the NAS committee's proposal and the conference, the international moratorium was observed; however, many commentators believe that this was due in great part to the list of distinguished scientists who agreed to support the moratorium. Judith P. Swazey *et al.*, *Risk and Benefit, Rights and Responsibilities: A History of the Recombinant DNA Controversy*, 51 S. CAL. L. REV. 1019 (1978).

141. Ira H. Carmen, CLONING AND THE CONSTITUTION: AN INQUIRY INTO GOVERNMENTAL POLICY MAKING AND GENETIC EXPERIMENTATION 93 (1985).

142. *Id.* Dr. Cline and his team claim that they were not trying to avoid regulatory authorities in the United States by performing the experiments abroad; rather, they said they chose to work in Italy and Israel because the incidence of beta thalassemia is higher there than in the United States. Gina Kolata, *Human Gene Treatment Stirs New Debate*, SCIENCE, Oct. 24, 1980, at 407.

143. The total amount of the canceled grants was in excess of $190,000. The NIH also placed stricter conditions on Dr. Cline when he applied for future grants. Marjorie Sun, *Cline Loses Two NIH Grants*, SCIENCE, Dec. 11, 1981, at 1220.

recent incident, one of America's leading molecular biologists, Dr. David Baltimore, has been implicated in the cover-up and use of falsified data concerning the effect of transferred genes on the human immune system.[144] Dr. Baltimore did not conduct the research in question, but he was the co-author of the paper in which it appeared, and he initially defended its contents.[145] Dr. Cline's failure to gain proper approval for his studies and Dr. Baltimore's initial reaction to the criticism of his paper are examples of incidents in which a scientist has been too involved in his/her research to be able to view the research objectively. Therefore, in order to benefit society, the application of genetic manipulation should be monitored by a governmental board or agency composed of members from all aspects of human life.

## V. The Present Regulatory System

The present system of regulation for rDNA technology began in 1974 when the NIH established the Recombinant DNA Advisory Committee (RAC). The RAC is composed of twenty-five members drawn from the fields of law, molecular biology, medicine, ethics, and the general public; its initial task was to develop procedural standards for NIH-funded rDNA experiments.[146] These standards, the Federal Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines), were published in 1976[147] and have since been revised.[148] The central focus of the NIH Guidelines is to prevent environmental contamination by the rDNA-altered organism used in the experiment. In general, the NIH Guidelines establish levels of physical and biological containment necessary for the safe handling of genetically altered organisms.[149] In cases where serious risk is presented, scientists must submit detailed data, including toxicity studies, to the RAC on the host/vector system that they intend to use.[150] The RAC makes its recommendation and then passes the

144. Philip J. Hilts, *Crucial Research Data in Report Biologist Signed Are Held Fake*, N.Y. TIMES, Mar. 21, 1991, at A1.

145. *Id.*

146. Naumann, *supra* note 35, at 65.

147. 41 Fed. Reg. 27901-27943 (1976).

148. 51 Fed. Reg. 16958-16985 (1986).

149. Physical containment refers to the procedure necessary to ensure that no material escapes the physical area in which experiments are conducted. The Guidelines establish four levels (p-1 through p-4) of physical containment. P-4 is the maximum control, requiring airtight experimentation areas accessed through glove ports. Biological containment, on the other hand, refers to the ability of the genetically altered organism to survive outside the special conditions maintained in the laboratory. Talbot, *supra* note 24, at 808-09.

150. Edward L. Korwek, *The NIH Guidelines for Recombinant DNA Research and the*

application on to the director of NIH for final approval.[151] Finally, the NIH Guidelines require an institution conducting even low-risk experiments to establish an Institutional Biosafety Committee (IBC) to ensure that the procedures established in the NIH Guidelines are followed.[152]

In 1984, the RAC realized that the initial guidelines had not fully taken into account the possibility of human applications of genetic manipulation. Therefore, it established the Human Gene Therapy Subcommittee[153] to explore the specific problems of human gene therapy. The Subcommittee proposed and the RAC approved a document titled "Points to Consider in the Design and Submission of Human Somatic-Cell Gene Therapy Protocols," which:

> formally requests . . . [a researcher to provide] information on a variety of topics that the Human Gene Therapy Subcommittee considers relevant to the task of deciding whether to recommend approval of a specific protocol for human gene therapy; implicitly, however, it imposes requirements on researchers seeking approval that go beyond the RAC Guidelines.[154]

In addition, human subjects in rDNA research experiments are covered by the general federal regulations concerning the use of human beings in all experiments.[155] Under these regulations, each research facility is required to establish an Institutional Review Board (IRB) to review protocols using human subjects.[156] Approval for such research is given only if the risk to the human participants is minimal or in proportion to the potential benefit from the protocol.[157] The human subjects or their legal representative must also give informed

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*Authority of FDA to Require Compliance with the Guidelines*, 35 FOOD DRUG COSM. L.J. 633, 636-38 (1980).

151. *Id.* at 638.

152. *Id.*

153. The subcommittee is composed of 15 members drawn from the RAC who serve either one, two, or three year terms. The staggered term system allows the composition of the subcommittee to rotate and thus not be overly influenced by any one group. Areen and King, *supra* note 85, at 151 n.5.

On February 10, 1992, the RAC voted unanimously to merge the subcommittee into the RAC. All gene therapy protocols will now be reviewed by the combined group. *The Blue Sheet*, FDC REPORTS, Feb. 19, 1992, at 7.

154. Areen and King, *supra* note 85, at 152. Examples of these additional considerations are that: 1) researchers are asked to confirm that patients will agree to at least three to five years of follow-up; 2) participants in the protocol be advised of the risks of withdrawing from the study after receiving genetically altered material; 3) researchers agree to notify NIH if any serious adverse effects occur; and 4) researchers agree to keep the identity of the patients and their families confidential.

155. 45 C.F.R. §§ 46.101 *et seq.* (1988).

156. Areen and King, *supra* note 85, at 151-52.

157. 45 C.F.R. § 46.111(a)(1), (2) (1988).

consent to the process.[158] Therefore, "[a]ny protocol for human gene therapy conducted at an institution receiving NIH research funds will need the approval of at least four different regulatory bodies before going forward: the local IBC, the local IRB, the RAC and the FDA."[159]

## VI. Problems with the Present System

This impressive array of regulatory authority is deemed necessary to protect the public at large and the individual research subjects from any possible ethical or ecological harm resulting from the use of gene therapy. Yet, in spite of all its internal checks and balances, the system has some serious problems. To begin with, the NIH Guidelines apply only to institutions that receive funding from the NIH.[160] In addition, the legal basis for the NIH's power to require compliance with the NIH Guidelines even for NIH-funded institutions is somewhat unclear. There are two main theories concerning NIH's power to enforce the Guidelines: 1) the NIH promulgated the Guidelines in accordance with formal agency rule-making procedures; therefore, the guidelines are to be treated as agency rules; and 2) the basis of the NIH's power is derived from the contract between the researcher and the NIH.[161]

In recent years, the contract theory has been gaining support based on a ruling by the District of Columbia Circuit Court of Appeals in *Foundation of Economic Trends v. Heckler*.[162] In *Heckler* the court indicated "that NIH approval of genetic engineering experiments is an explicit condition . . . [that] must be satisfied before a scientist can receive federal funds for recombinant DNA research."[163] Under this approach, as in contract law, the non-occurrence of a condition (compliance with the Guidelines) prevents the promisor's (NIH's) duty (funding) from arising.[164] The situation is further complicated by the fact that NIH has never officially stated the legal authority on which the NIH Guidelines are based.[165] The basis for the NIH's power to enforce the Guidelines is important because, without proper authority, the NIH Guidelines are open to

158. 45 C.F.R. §§ 46.111, 46.116 (1988).
159. Areen and King, *supra* note 85, at 155.
160. Areen and King, *supra* note 85, at 152.
161. Korweck, *supra* note 150, at 636.
162. 756 F.2d 143 (D.C. Cir. 1985).
163. Naumann, *supra* note 35, at 67-68.
164. Korwek, *supra* note 150, at 636.
165. Korwek, *Recombinant DNA and the Law: Review of Some General Legal Considerations*, 15 GENE 1 (1981).

constitutional challenge.

Another problem with the present regulatory system is that the NIH is not the only government agency involved in the regulation of genetic engineering. Other agencies with regulatory concerns relating to rDNA are the Food and Drug Administration (FDA), the Environmental Protection Agency (EPA), the Department of Agriculture (USDA), the National Science Foundation (NSF), and the Occupational Safety and Health Administration (OSHA). While many of these agencies have incorporated the NIH Guidelines into their individual regulatory schemes, the potential for conflicting decisions is still present. The following analysis will concern only the interaction between the FDA and the NIH in the regulation of gene therapy.

Beginning in 1979, the FDA asserted that its regulatory powers extended to all new drugs and methods of producing new drugs.[166] The FDA interpreted this to mean that even when a drug made by conventional means had been approved for use, the same drug when made by another company or by different means would be a "new drug." Therefore, generic drugs or drugs produced by rDNA processes were to be included under the FDA's pre-marketing review process.[167] The United States Supreme Court ultimately upheld the FDA's extension of power.[168] In addition, the FDA claims authority to regulate human gene therapy through its power to regulate all clinical pharmaceutical testing.[169] This proposition presents two problems for the scientific community and the public at large. First, the FDA's enabling statute gives the agency power to regulate drugs and products used in clinical testing when they move in interstate commerce.[170] Therefore, it is possible to question the FDA's authority to regulate gene therapy if the rDNA product given to the patient has not moved in interstate commerce. Second, some commentators question the FDA's ability to require compliance with the NIH Guidelines.

Under the basic principles of administrative law, an agency cannot promulgate substantive or interpretive regulations unless the reg-

166. Naumann, *supra* note 35, at 70.

167. Naumann, *supra* note 35, at 70.

168. United States v. Generix Drug Corp., 460 U.S. 453 (1983). In *Generix*, the Supreme Court was presented with a manufacturer that claimed its generic product was not subject to FDA review because the active ingredient had already received FDA approval. The Court held that the term "new drug" applied to both the active and non-active elements of a drug.

169. Naumann, *supra* note 35, at 71.

170. Naumann, *supra* note 35, at 71.

ulations advance some provision of the agency's enabling statute. If FDA were to incorporate the NIH Guidelines, the commentators suggest that the only logical way to do so would be under the Good Manufacturing Practices regulations (GMP) of the Food, Drug and Cosmetic Act.[171] The GMP regulations carry the force of law and cover a wide range of practices, including those conducted in laboratories as well as those conducted in packaging and labeling.[172] The problem with incorporating the NIH Guidelines into the GMP regulations is that the objectives of the two systems are quite different.[173] The GMP regulations are designed to carry out the overall goal of the Food, Drug and Cosmetic Act — purity of food and drugs to ensure the safety of the people who use them — while the NIH Guidelines were established to "specify practices for conducting basic research and have nothing to do with assuring the identity, strength, quality and purity of the products of the technology."[174] Therefore, it appears that FDA would be going outside its administrative mandate in attempting to require compliance with the NIH Guidelines.

## VII. Attempts to Amend the Present System

The different purposes of the NIH and the FDA highlight the potential for conflict in regulating human gene therapy due to the overlapping jurisdiction of the agencies involved. These jurisdictional conflicts will also lead to inconsistent regulations being issued by the different agencies. Therefore, it is clear that some method of resolving the present difficulties in regulating genetic engineering must be found. The government took steps in this direction when the White House Office of Science and Technology created the Biotechnology and Science Coordinating Committee (BCSS) in 1985.[175] The BCSS was designed to provide all the agencies regulating genetic engineering with a forum in which they could discuss the scientific and regulatory problems created by the new technology. In this way, general scientific understanding could be reached and all agencies would be able to regulate even-handedly. The problem with the BCSS is that it was given no power to resolve interagency disputes or to enforce its recommendations.[176] Therefore, the BCSS lacks the authority to be

171. Korwek, *supra* note 150, at 639-40; *see also* 21 U.S.C. §§ 301 *et seq.* (1988).
172. Korwek, *supra* note 150, at 641-42.
173. Korwek, *supra* note 150, at 642.
174. Korwek, *supra* note 150, at 643.
175. Naumann, *supra* note 35, at 79-80.
176. Naumann, *supra* note 35, at 79-80. When the concept for a biotechnology review

a centralized regulatory overseer for the developing applications of biotechnology.

Another possible solution to the regulatory problems created by genetic engineering is to elevate the status of the RAC and Human Gene Therapy Subcommittee to a position in which they could oversee all aspects of genetic engineering. This also creates some problems, specifically for the medical applications of genetic engineering, because the RAC and its subcommittee do not have a mandate to address the ethical issues presented by either germ-line gene therapy or enhancement genetic engineering.[177] Therefore, Adrienne Naumann and other commentators have proposed the establishment of a new 'super agency' or commission created in the mirror image of the RAC, but with rule-making authority and the power to settle interagency disputes.[178]

Congress also became directly involved in the monitoring of biotechnology in 1985 when it enacted legislation allowing for the creation of a Bioethics Board (BEB).[179] The BEB was modeled on the Office of Technology Assessment and was comprised of twelve members (six from each House of Congress — an equal number from each party).[180] The function of the BEB was to provide Congress with a continuing report on the ethical issues arising in the new field of biotechnology.[181] To aid the BEB in this task, the board was to appoint a fourteen member Biomedical Ethics Advisory Committee (BEAC) composed of four scientists, three doctors, five ethicists, and two members of the public with an interest in biomedical ethics.[182] The promising potential of the BEB and BEAC all came to naught, however, when the BEAC could not agree on a replacement for one of the original members who had died before the first meeting.[183] Finally, Congress withdrew funding for both the BEB and BEAC in 1989 and, while the legislation is still on the books, no progress can be made without funding.[184]

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board was first proposed in 1984, the board would have had the power to settle such disputes. Under the original plan, the Biotechnology Science Board (BSB) would have had a structure similar to the RAC and would have assumed many of the RAC's duties. Culliton, *New Biotech Review Board Planned*, SCIENCE, Aug. 1985, at 736; *see also* 49 Fed. Reg. 50,905 (1984).

177. Areen and King, *supra* note 85, at 156.

178. Naumann, *supra* note 35, at 92-93; *see also* Culliton, *supra* note 176, at 736.

179. 42 U.S.C. § 275 (Supp. 1990). The BEB was approved by Congress over the veto of President Reagan. Areen, *supra* note 29, at 171.

180. Areen and King, *supra* note 85, at 156.

181. 42 U.S.C. § 275(c)(1) (Supp. 1990).

182. 42 U.S.C. § 275(d) (Supp. 1990).

183. Areen and King, *supra* note 85, at 156.

184. Areen and King, *supra* note 85, at 157.

The collapse of the BEB and BEAC in 1989, combined with the inability of the BSCC to resolve interagency disputes, creates a serious obstacle to any unified policy of regulation for genetic engineering. Without a unified and consistent policy of regulation, the progress of genetic engineering, especially human gene therapy, may be slowed by overregulation. It is essential for the development of human gene therapy, therefore, that the government overcome the obstacles that it has created and devise a unified system of regulation. This could best be accomplished by Congress through the refunding of the BEB and BEAC. The BEB's function could be expanded to include a review of the present regulatory system and the development of options for streamlining the regulatory process. In this way, the BEB could address both the ethical and regulatory problems presented by the continued application of human gene therapy. Such a committee would be endowed with the best elements of the present RAC and the ability to resolve interagency disputes that is lacking from the BSCC.

Present members of the RAC and members of the agencies currently regulating genetic manipulation would be ideal candidates for positions on the BEAC. This would ensure that the decisions reached by the BEAC would be the work of scientists, ethicists, and the general public. In addition, the overall recommendations of the BEB would carry the weight of a congressional committee report. Congress could then enact the necessary legislation to implement the BEB's recommendations. Once the new system of regulation was in place, the BEB would continue to report to Congress on the progress of the new system and the evolving concerns presented by the development of human gene therapy. The end result of such a process would be a unified system of regulation for gene therapy that would avoid the problems presented by overlapping agency jurisdictions and a permanent Congressional committee to oversee the regulatory process and resolve any regulatory or ethical problems that arise in the development of human gene therapy. Even if the BEB recommended the continuation of the present system of regulation, the BEB could still function as the information gathering and reporting mechanism that Congress originally intended it to be. A functioning BEB would ensure that Congress is kept well-informed about the difficult issues that will arise as human gene therapy develops. Therefore, it is clear that Congress should redesign and re-fund the BEB

and BEAC, for it is through the operation of these two boards that the government will best be able to respond to the challenges of biotechnology and human gene therapy.

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